of an adverse reaction to the vaccine; benefits, however, include not only the likelihood that a vaccine will protect against a disease, that is, its efficacy, but also that it will ameliorate the severity of the disease to be prevented. Greater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign. Furthermore, "benefit" may extend not only to the recipient of the vaccine, but in some cases to society at large.

The risks versus the benefits of the vaccines covered in this report are, like other features of these vaccines, very diverse. Standards of safety must again be individualized for each kind of vaccine. For example, tetanus toxoid is among the safest of all vaccines and its benefits are enormous. Attempts to reduce its reactivity further must not, therefore, jeopardize its efficacy. Although the benefits of pertussis vaccine in infants have occasionally been questioned, the preponderance of expert judgment is definitely favorable. But this vaccine is highly reactive and very justifiable attempts to reduce its reactivity by purification are virtually thwarted by the dependence of the assessment of efficacy upon a mouse protection model which must be linked to clinical trials to confirm its validity. Despite the vaccine's hazards, therefore, attempts to modify it to improve its tolerance are difficult with present knowledge.

Risk/benefit assessments vary not only between one generic group of vaccines and another, but within a generic category, each product must be assessed individually for its special features that vary from the norm. In addition, some products were modified without updated evidence of their clinical efficacy. In some very uniform vaccines, such as tetanus toxoid, a relatively minor change in production to achieve greater purfication or a decreased concentration of toxoid to reduce reaction rates was examined by the Panel very critically because of the need to ensure that the vaccine performed at its expected high level of protection.

The concept of risk/benefit also includes the public's as well as the individual's protection. A vaccine that produces considerable discomfort and sometimes even severe general reactions is more acceptable if the protection it affords the individual also results in protection of the community by reducing contagion. Such is the case in vaccination against pertussis, a contagious disease particularly dangerous to very young infants but dramatically controlled by a rather reactogenic vaccine. In contrast, cholera vaccine exerts little or no effect on the prevalence or spread of the disease and acceptance of its reactions is limited.

(2) *Adjuvants.* In the course of its deliberations, the Panel was informed by the Bureau of Biologics of the results of studies of the effect of injection of aluminum adjuvants into special strains of white mice which have a very high natural incidence of fibrosarcoma of the skin. Such mice have been used in some screening studies for the oncogenicity of certain drugs. The experiments showed some enhancement in the rate of formation of fibrosarcomas in the mice that received aluminum adjuvants. The Panel asked for expert interpretation of the design and results of the mouse studies by scientists from the National Cancer Institute and Roswell Park Memorial Institute. These consultants concurred with the Panel in their opinion that the mouse findings were indeed reliable for the design of the experiments but that the significance of the findings for man could not be assessed from this model alone and that studies in other mammalian species should be made.

The Panel therefore surveyed data in man on fibrosarcomas in different populations from various cancer registries. These show that fibrosarcoma is a rare tumor, the incidence increasing sharply in old age. Cohorts were analyzed who were probably exposed to aluminum adjuvants, such as males born around 1920 who probably received immunizations during World War II, whereas the women generally did not. No increased rate of sarcoma in males in that cohort was detected. Because most Canadian vaccines do not contain aluminum adjuvants, mortality rates in Canada were compared with those in the United States for fibrosarcomas. Rates of connective tissue tumors were slightly higher among United States than Canadian males, but the rates for females were similar. The data did not disclose any major differences that would cause concern over the use of aluminum adjuvants whose benefits are considered to be of major value in the primary immunization of children with DTP vaccines. The Panel encouraged further studies on adjuvants, especially retrospective studies in humans, but did not consider that their recommendations for the safety and efficacy of DTP vaccines containing aluminum adjuvants should be modified at this time.

(3) *Liability and legal problems.* Almost any clinical investigation to improve well established and highly beneficial vaccines, or to assess more accurately their current reaction rates, is frustrated by the threat of malpractice suits and claims for damages against manufacturers. Physicians who administer vaccines as well as those who produce them feel threatened when reporting adverse reactions, even when the vaccine has been prepared and used in accordance with government regulations and recommendations. Moreover, some reactions are intrinsic to the process of human immunization and range from psychic trauma to fatal idiosyncratic reactions that are extremely rare and are an unavoidable hazard of introducing foreign substances into humans.

The United States has been backward in its failure to deal with the risks and responsibilities of immunization. Several European countries and Japan have established a public compensation system under which their governments have accepted responsibility for the recognized hazards of immunization. Some of these laws provide for compensation from public funds to patients suffering damage from vaccinations that are recommended by competent authorities. Damages have been paid as pensions.

The differences between the primary responsibility of the manufacturer and the ultimate responsibility of the State should be distinguished. The former should comply with the regulations of production and marketing procedures. If these obligations are fulfilled and the vaccine is administered correctly, responsibility for immunization accidents should rest with the official agencies recommending them. Unlike many other countries, the United States has not dealt adequately with this issue of immunization, and attempts to improve vaccines further will be hampered. Furthermore, collection of data to establish the efficacy of some of the current licensed products may also be hampered by this deficiency of public policy in the United States.

b. *Determination of efficacy*—(1) *The diverse immunologic actions of the vaccines.* The various vaccines that have been lumped together for this Panel's review are so diverse that standards of efficacy that apply to one may not apply to another at all. Progress in immunology is far greater in areas relevant to the effects of some vaccines compared to others. For diseases in which immunity depends upon specific antibodies which either neutralize toxin or which opsonize bacteria and lead to their prompt destruction within phagocytes, induction of such antibodies

correlates well with protection, and the measurement of such antibodies may reflect efficacy quite faithfully.

In many other kinds of antibacterial immunity, however, survival of organisms within cells after ingestion is a particular feature of the host-parasite contest. In these infections the role of cellular immunity is critical. Diseases such as tuberculosis and typhoid fever are illustrative of infections that may be considered intracellular as well as extracellular. Our knowledge of immunity in such diseases still awaits greater understanding of the cell-mediated defense process. The effects of vaccination therefore remain empirical in these diseases and can be established at present by field trials alone. In pertussis, for example, the relative roles of humoral and cellular immunity are not at all clear, and the antibodies that can be measured may or may not be protective.

Finally, protection against a disease such as cholera has been proven in recent studies to depend primarily upon the prevention of the attachment of the cholera vibrios to the surface of intestinal epithelial cells. The solution of this problem appears more feasible than the more complex antibacterial immunity of diseases like typhoid fever.

(2) *Establishing standards of efficacy.* It should be apparent that a standard of efficacy must be applied separately to each vaccine according to current expectations of its performance. For example, for the prevention of tetanus an almost perfect performance can be expected. Moreover, its efficacy can be quite accurately assessed by serum antitoxin levels. For diphtheria, the standard of efficacy is also high, but there is less certainty as to what level of antitoxic immunity constitutes adequate protection because strains of diphtheria may vary greatly in the amount of toxin they can produce, and absolute immunity based on a given level of antibody is less predictable.

A major dilemma repeatedly faced by the Panel was the decision whether to place a given product in Category I or Category IIIA. The law requires that each product be proven to be both safe and effective in man; for many products, licensed prior to the current, more stringent legislation, specific data related to efficacy are not available. Even in the absence of such data, however, the Panel has little doubt that the efficacy of tetanus and diphtheria toxoids are satisfactory because it is reasonable to infer that if they were not satisfactory, the remarkable reductions in tetanus and diphtheria associated with widespread use of these vaccines surely would not have occurred. Moreover, the techniques of production suggest that they should be efficacious.

But the charge to the Panel was to examine each licensed product from the standpoint of the scientific evidence that each is both safe and effective in humans. The various toxoids placed in Category IIIA by the Panel are believed to be entirely acceptable in terms of safety. The Panel believes that many are effective, but in the absence of recently obtained proof in humans for certain specific products, the Panel's charge to affirm the effectiveness of individual products could not allow a Category I assignment.

The feasibility of obtaining efficacy data is technically simple in the case of the toxoid vaccines (tetanus and diphtheria) because serum neutralizing anitbodies are readily measureable and these reflect efficacy accurately. Blood samples from relatively small numbers of healthy volunteers (see prototype model for study with 20 to 40 individuals) who receive immunization can therefore establish efficacy. Obtaining blood samples from healthy volunteers receiving licensed vaccines, particularly children and infants, is a problem currently complicated by recent regulations on informed consent. However, the difficulties which may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization. For these reasons, the Panel recommends that products for which the human data requested are not available be assigned to Category IIIA.

In the case of pertussis, the situation is peculiar. Though the vaccine is a very effective one, it is quite crude, consisting either of killed whole cells or of a soluble product of the organism. The nature of immunity is unknown. The disease has almost disappeared in the United States, making field trials, at least in this country, impossible. The standard of efficacy is tied to a highly artificial mouse model of protection—one that bears essentially little similarity to the natural disease in man. Yet the last successful field trials conducted decades ago are tied to current products whose toxicity represents the major concern about the vaccine. Any move to make the vaccine safer by modifying it is fraught with the danger of altered efficacy which cannot be adequately assessed without an extensive field trial.

The plague and cholera vaccines place the Panel in the apparently inconsistent position of classifying them as effective without the extensive efficacy data that are available for other vaccines. These vaccines are of decidedly limited value. At the same time, the Panel demands of tetanus updated on antibody levels when relatively small changes in the vaccines have been introduced recently into the manufacturing process.The expectations of efficacy from the current plague and cholera vaccines are obviously quite different from those expected from tetanus.

Finally, standards for judging efficacy of currently available BCG vaccines are far from satisfactory. No reliable animal model or immunologic test has yet been discovered that accurately reflects human immunity; nobody can prove that the live vaccine strains have remained unchanged by repeated passage in the laboratories where they are maintained; and only new field trials that are in progress but are several years from completion can determine efficacy. Even then such efficacy would have to be related only to the strains used in the trial. Nonetheless, decisions have to be made based on past performances and to some degree upon the assumption that the strains of current vaccines are retaining their immunizing power. Lacking other alternatives, the decision for efficacy was made by the Panel with full knowledge of the assumptions that were made.

(3) *Extrapolation of data from the use of combined vaccines.* Practical considerations in the evaluation of efficacy for some products when data were unavailable made it desirable and sometimes necessary to extrapolate from data on the use of combined vaccines. This approach appears to be logical and valid, particularly for diphtheria, tetanus, and pertussis vaccines, because of the wide use of the combined diphtheria, tetanus, and pertussis vaccines and the endorsement of this immunization practice by all leading biomedical experts in this country. Accordingly, the Panel made use of the following extrapolation models whenever it seemed appropriate because of the availability of the data:

1. Diphtheria tetanus and pertussis (DTP) could provide efficacy data for pertussis (P) (but not for diphtheria (D) and tetanus (T) due to adjuvant effect of pertussis).

2. Tetanus and diphtheria (Td) could provide efficacy data for T and also possibly for diphtheria and tetanus (DT) and D if the small 2 Lf dose of DT in Td proved adequate. Caution would be necessary in extrapolating Td data in adults to children 6 years of age or younger.

3. DT could provide efficacy data for D, T, and for the T component of Td.

Combined product available	Would provide efficacy data for:
DTP	P
Td	DT [1] D [1] T
DT	D T Td (T-only)

[1] If response of 2 Lf Diphtheria toxoid were satisfactory, the larger amount in "D" products could be assumed satisfactory.

(4) *Patient participation, informed consent, and clinical trials.* When sufficient data were not available from which to determine efficacy, the Panel had to consider the feasibilty and cost benefit of the required further clinical investigation. Such factors stimulating the Panel's desire for more data were: (i) Changes in the manufacturing process, the concentration of antigen, the purification of the product, or the additions of preservatives or adjuvants; (ii) the dependence of some manufacturers upon clinical data establishing the effectiveness of the same vaccine made by others; (iii) possible changes in the state of immunity of the population and secular changes in the epidemiology of the disease; (iv) the need for better products or immunization schedules to increase efficacy or decrease reactivity.

On the other hand, the Panel was mindful of the growing difficulties of obtaining participants and informed consent for clinical trials—even those as simple as obtaining a few samples of blood per patient by venipuncture. For primary immunization trials, the need to obtain consenting subjects who have no prior immunity imposes a further stringent limitation. If clinical trials were to require more than an assessment of humoral responses, the inability to evaluate protection against a challenge of natural disease in this country (such as in the case of tuberculosis or pertussis) made insistence upon such data unreasonable. The dilemmas of inadequate clinical data to judge efficacy versus limited access to such data led to productive discussions and workshops with manufacturers and the Bureau of Biologics to establish efficient and relatively standard protocols which would supply the required data from minimal numbers of participants and at minimal costs. The Panel's general recommendations contain suggestions arising from these conferences.

(5) *Animal models.* Animal models of the human diseases in which vaccines may be accurately and reliably assayed for safety and efficacy would solve many problems of clinical investigation and human trials. The Panel found this need particularly cogent in the case of pertussis and tuberculosis in which animal models were inadequate and field trials not feasible. In these instances recommendations that vaccines be classified in Category IIIA to obtain further proof of safety and efficacy will be greatly handicapped unless animal models are developed which correspond closely to the human disease counterpart.

(6) *Administrative problems.* Several administrative problems had to be solved by the Panel to carry out its charge and mission. Some licenses had been held on products which the manufacturers had not marketed for many years. Some of these products were intended to be used only when the vaccine was combined with others (for example, monovalent diphtheria toxoids). Some antiserums (equine diphtheria antiserum) and some toxins (diphtheria toxin for Schick testing) were considered useful for limited purposes only. They might be in limited supply, therefore, unless publicly subsidized. During the course of the Panel's review, licensed products were updated because of modifications, and license applications were amended to replace outdated products (for example, plague vaccine).

(7) *Related issues.* Careful attention was given to the opinions and policies of other governmental agencies and professional societies concerning the safety, efficacy, and recommended usage of the vaccines reviewed. The Panel was mindful that its decisions were concerned primarily with assessing evidence of safety and efficacy of the vaccines rather than determining either public health or clinical practice policy governing their usage. It was gratifying, however, that very few significant differences of opinion were encountered among recognized authorities. The most divergent opinions related to the issue of the efficacy of the BCG vaccines and reflected the need to establish whether or not prolonged storage and passage of the seed strains in laboratories had led to changes in their efficacy. Limited enthusiasm for the use of BCG by public health authorities in the United States as a means for the control of tuberculosis had to be weighed against: (i) Evidence of efficacy; (ii) alternative strategies for control; and (iii) the right of manufacturers to produce and physicians to use a vaccine, if effective, in some parts of the world and in some populations of the United States with unusual risks of exposure to tuberculosis. Althogh some would have preferred a "Category III" classification for BCG, requiring updated clinical data of efficacy, the feasibility of obtaining such data in the ensuing several years appeared remote and unnecessary at this time when weighed against the favorable evidence for BCG. The Panel was faced with having to make an "effective" versus "ineffective" judgment on the basis of the evidence at hand and the evidence, although incomplete, clearly called for a judgment of effectiveness.

3. *General recommendations*—a. *Support for widespread immunization programs.* Universal active immunization for the prevention of tetanus, diphtheria, and pertussis should be accomplished to take full advantage of the great effectiveness of these vaccines and to obviate the inherent risks, cost, and effort of passive immunization which is incompletely effective in the first two diseases and not effective in the third.

b. *Liability legislation for immunization.* Assessment of the safety of vaccines requires improved procedures for reporting adverse reactions. This in turn requires the development of a more enlightened public policy which includes acceptance by the U.S. Government of responsibility for the recognized and unavoidable hazards of immunization.

Legislation is urged that will provide compensation from public funds to individuals suffering damage from vaccinations that are recommended by competent authorities, carried out with vaccines that passed official safety and efficacy review, and that were administered by recommended techniques. Such legislation will not only greatly improve assessment of safety but will also enhance collection of the data necessary to establish efficacy by reducing the professional liability issues in clinical investigation of vaccines.

c. *Improved efficacy of clinical investigation.* The Bureau of Biologics should offer guidance to manufacturers with regard to recommended protocols which would help to provide adequate clinical data for assessing vaccine efficacy. Because of the increasing difficulties in obtaining informed consent to conduct studies on normal individuals, even studies requiring no more than serial venipunctures, it would be most efficient and economical to develop protocols that would provide required information with the fewest numbers of participants and specimens. These considerations are especially appropriate in studies involving children. Cooperation among manufacturers and the Bureau of Biologics should be promoted to adopt relatively standardized protocols that might set minimum limits to the numbers of individuals required to achieve

statistical strength of data and appropriately controlled conditions, laboratory methods, and population groups.

Currently there is a conflict between the public's need for precise data regarding the safety and efficacy of immunization programs and the rights of the individual, both in terms of experimental risk and privacy. Despite the need to protect the privacy of the individual, a mechanism should be developed that would provide means of access for authorized investigators to demographic and health data on individuals in order to conduct long-term followup studies of immunization procedures.

d. *Improved production procedures.* Some standards of purity, immunogenicity, and immune responses for well-established vaccines are based upon old-fashioned methods that should be updated by more sophisticated techniques made possible by advancing scientific knowledge. Efficacy and safety should be assessed and defined in terms of more modern standards of quantitative immunobiologic testing, chemical purification, and clinical evaluation. The motivation and impetus to accomplish this is unlikely to come spontaneously from pharmaceutical manufacturers unless review of vaccine licensure is conducted periodically. In addition, workshops should be promoted regularly by the Bureau of Biologics to encourage progress in methodology and to coordinate further efforts at standardization.

e. *Research priorities*—(1) *Animal models.* There is great need to develop animal models that accurately predict vaccine responses in man. Throughout the Panel's review, one of the most frequently recurring problems was the need to minimize our dependence on the laborious collection of expensive and often virtually unobtainable clinical data in order to determine efficacy. Manufacturers are not primarily responsible to implement the quest for animal models, and the development of such models will require public research support.

(2) *Laboratory tests and procedures.* Increased emphasis is needed on the development of laboratory tests and procedures that reflect vaccine efficacy with sufficient accuracy so as to minimize the need for field trials. Improved immunologic tests, the use of tissue culture assays, and relatively simple, reliable, and low-risk clinical procedures, such as skin tests, would simplify clinical investigation of vaccine efficacy.

(3) *Collaborative and cooperative studies.* Collaborative and cooperative studies should be encouraged particularly when such group efforts at collecting data may reduce the cost and effort and increase the availability of opportunities for clinical investigation, or may resolve quickly and efficiently such issues as dose schedules and the frequency and intervals of injections of vaccines within a generic group that are comparable in potency.

(4) *Areas of limited knowledge concerning effective vaccines.* Support is needed for research in areas where knowledge of the mechanisms of immunity is limited. It is possible that the judgment of a vaccine as safe and effective may actually discourage research by lowering the apparent priority for the need to improve the vaccine. In diseases such as pertussis, typhoid fever, and tuberculosis, the mechanisms by which immunity is produced and the specific antigens that are responsible for the induction of immunity and for reactogenicity are poorly understood. Further research efforts to reduce the toxicity of these vaccines and to improve their effectiveness will require specific public support.

(5) *Increased efficiency of effective vaccines.* Support should be available for clinical investigation in areas of vaccine research where it is likely that further progress can be made even where a high degree of vaccine efficacy already exists. An example would be the improvement of the already very safe and effective tetanus vaccines by reducing the number of injections required to achieve primary immunization.

(6) *Unmet needs.* Finally, rearch is needed to fulfill unmet needs in protection against bacterial infections. Streptococcal, staphylococcal, gonococcal, hemophilus, and pseudomonas infections, to name but a few, are potentially preventable by immunization. Morever, there are some products that are needed and can probably be prepared but are not available now, such as botulinus human immune globulin and diphtheria human immune globulin.

f. *Assurance of vaccine availability.* Close surveillance is necessary of certain vaccine products whose ongoing production in the United States may be discontinued or suspended for a commercial reasons despite current or potential needs. Diphtheria toxin for Schick testing and equine diphtheria antitoxin for the treatment and passive immunization of diphtheria are two examples. Continued interaction between the Bureau of Biologics and the Centers for Disease Control should be encouraged to ensure government stock piling of required products that are no longer produced commercially.

In addition, some products are produced solely by foreign firms. The Istituto Sieroterapico Vaccinogeno Toscano Sclavo pharmaceutical firm in Italy is a major source of diphtheria antitoxin, and the status of diphtheria antitoxin produced in the United States is uncertain. Connaught Laboratories of Canada is the only producer of trivalent botulinus antitoxin. Furthermore, a major vaccine produced by a single domestic firm represents an inherent danger, in that the public is dependent upon a limited source without well-defined mechanisms for the control of production and supply.

Public policy needs to be formulated more thoroughly in the entire area of production and supply of vaccines. Prospective planning and negotiation between public agencies and the pharmaceutical industry should be established as a process by which to ensure vaccine availability when the market alone is inadequate to accomplish this end. Consideration should be given to the establishment of a National Vaccine Commission which can address itself to the solution of these problems.

g. *Improved reporting of adverse reactions.* At present, there are virtually no standards set for what constitutes untoward reactions to vaccines except their most severe and dire complications; therefore, it is difficult to document the actual reactogenicity of some products. Standards for "threshold reactions" above which reports are required need to be established for each generic group of vaccines. The Study Commission on Drug Use, which is studying adverse drug reactions, should be urged to consider reactions to biological products as well.

h. *Improved labeling.* Review of the labeling of products submitted to the Panel identified a number of deficient areas in which substantial improvement should be made. A standard for adequate labeling along the lines outlined by the generic labeling statement of the Panel should be adopted so that the accuracy and readability of all labeling can be brought to an optimally useful level.

i. *Improved administrative procedures*—(1). *Periodic review of all licensed vaccines.* Periodic review of all licensed vaccines should be carried out to assure that the safety and efficacy of these products are kept current and that standards of production and assay are modernized.

(2) *Limited term for vaccine licenses.* By limiting the period for which

vaccines may be licensed, all products, old and new, will be assured regular review. Furthermore, new vaccines that have only limited evidence of efficacy or for which the clinical efficacy data needs to be extended by further experience (situations in which we now assign "Category IIIA," i.e., insufficient data but probably effective) should be provisionally licensed for only limited periods of time within which additional data can be generated.

(3) *Revocation of licenses for nonmarketed vaccines.* Some products that have not been marketed for many years are still licensed, and it is not known whether they would still qualify as safe and effective products if and when production is resumed. Some products have never been marketed in the form for which they were licensed. In the light of current efficacy review standards, it would be better policy to revoke such licenses and require reapplication when necessary.

(4) *Consistency of efficacy data.* Protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product and should employ standard tests, standard procedures for conducting tests, and standard reference sera. It would be advantageous to develop industrywide, consistent, standardized guidelines for adducing required data. Such standardized procedures may need review and updating periodically, as new improved laboratory tests become available.

j. *International cooperation.* The Panel recommends that international coordination of vaccine standardization and assessment of safety and efficacy be encouraged through groups such as the World Health Organization, the International Association for Biological Standardization, and between ministries of health of various countries. In many instances the assessment of vaccine efficacy may be possible only in those countries where an opportunity for field trials may exist.

k. *Role of review panels.* Judging from the experience of the Panels during their reviews, their current roles as advisory groups should be extended so that they may continue to serve to help assess future safety and efficacy issues that arise with new or improved vaccines.

l. *Privacy of panel sessions.* The Panel has had little problem in performing its functions at open sessions and believes that closed sessions are necessary only to protect the rights of confidentiality to which license submissions are entitled. The Panel also has had no objection to having its sessions taped and recorded.

m. *Transcription policy.* The cost/benefit of verbatim transcription of the entire deliberations of the Panel, especially those that lead to a documented report, is, however, very limited. Verbatim transcription of the vast amount of tedious and noncontroversial detail covered in reviews is enormously wasteful, inhibits free, relaxed, and creative discussion and exposes Panel members to the risk of remarks and opinions that may be only tentative and that may be quoted out of context.

4. *Summary of unresolved problems.* In concluding its report, the Panel deems it important to call attention to some of the major unresolved problems that have made its advice and decisions most difficult and that will continue to hamper the assessment and the improvement of the safety and efficacy of vaccines.

a. Emphasis upon proof of efficacy and upon critical standards of the scientific quality of vaccine data may inhibit the motivation to modify and improve current vaccines and to introduce new ones. If rigid and critical standards are to be set and met, much effort should be put into finding efficient and effective ways to encourage and expedite the conduct of such research.

b. The complexity of the legal and administrative procedures deemed necessary to ensure the protection of the rights of individuals participating in clinical investigations impose serious restraints to the acquisition of vaccine efficacy data, because such studies are usually undertaken in normal individuals and often, in the case of universally administered vaccines, in relatively low risk groups. Public policy will have to be formulated to provide incentives to both clinical investigators and participants to engage in the carefully designed field trials and other controlled experiments that are now required. The U.S. public should share as a whole in the responsibility to participate in such studies. As previously noted in section 2.b.(2) of this preamble, the difficulties that may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization.

c. Standards of efficacy will have to be evolved for products that are not amenable to clinical trial (e.g., botulism antitoxin).

d. Emphasis upon the individuals' rights of privacy of personal health data can conflict with the public's need for data on immunizations which requires access to health records. Specific exceptions will have to be written to the laws protecting confidentiality of public health information, which is now regarded as private.

e. Finally, the glaring absence of a coordinated national immunization policy that would efficiently implement and expedite vaccination procedure and vaccine development, production, and supply is now apparent. Such a policy should be formulated without further delay so that future decisions on vaccine safety and efficacy can be made with greater assurance of public acceptability and support.

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